Pathology of B-Cell Lymphomas: Diagnosis and Biomarker Discovery

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Abstract

The diagnosis of B-cell non-Hodgkin lymphomas has changed significantly over the past few decades as new immunophenotypic markers, molecular subtype classification schemes, and novel biomarkers have emerged. Meanwhile, there has been an increasing emphasis on individualizing treatment approaches in accordance with a biologic heterogeneity that has been uncovered within many of the individual B-cell lymphoma entities. The application of high-throughput genomic sequencing to B-cell lymphomas has yielded large amounts of valuable information. The data encompass discoveries essential to an understanding of pathogenesis, clonal or tumoral evolution, and identification of biomarkers that may be useful for prognostic or therapeutic considerations. The following review discusses several of the more common, primarily tissuebased B-cell lymphomas, with a focus on pathologic classification and certain phenotypic characteristics or genetic lesions that apply to refinement of diagnosis and therapy.

Keywords

B-cell lymphoma · Biomarker

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1 Introduction

B-cell lymphoma diagnosis has conventionally incorporated morphologic, immunophenotypic, and genetic findings for classification into specific disease categories. Despite this, the clinical behavior within each B-cell lymphoma subtype is variable and reflects a biologic heterogeneity that is increasingly recognized with the application of unbiased molecular characterization. Recent discovery of new biomarkers has led to improvements in diagnosis and prognosis in B-cell lymphomas. Massively parallel sequencing technologies have identified recurrent mutations that target important cellular pathways, and this has deepened our understanding of the oncogenic mechanisms of many of these neoplasms. Aside from providing insights into pathogenesis, identification of biomarkers that might provide clues to new therapeutic options or targeted therapies with lower toxicity would be of great benefit to patients with B-cell lymphomas. An additional benefit of useful biomarkers is that they might serve to predict disease course, in order to inform individualized treatment decisions. This review will cover some of the more common, primarily tissue-based B-cell lymphomas, progressing from small B-cell entities to the diffuse aggressive B-cell lymphomas. Pertinent pathologic features and current classification issues will be addressed along the way, including phenotypic (Table 1) and genetic considerations for diagnosis and disease management. Potential biomarkers that have surfaced over the last few years will be considered along with each entity, in light of the feasibility of application in routine clinical settings (Table 2). Finally, a discussion of perhaps the most promising discoveries out of next-generation sequencing studies will provide a framework for ongoing literature review as the field advances.

Table 1 Expected immunophenotype of selected B cell non-Hodgkin lymphomas

	Expected immunophenotype
Follicular lymphoma	CD19+, CD20+, IgM ± IgD, monotypic sIg+, CD10+, bcl-6+, bcl-2 ±, HGAL, LMO2; associated with CD21+/CD23+ follicular dendritic cell meshworks
Lymphoplasmacytic lymphoma	CD19+, CD20+, monotypic sIg+, IgM, CD22+, CD79a+, CD5 ∓; plasma cells have monotypic cytoplasmic Ig
Mantle cell lymphoma	CD19+, CD20+, monotypic sIg+, IgM ± IgD, CD5+, CD23− or weakly+, cyclinD1+, SOX11± , LEF1 −
Diffuse large B cell lymphoma, nos	CD19+, CD20+, monotypic sIg+ or absent sIg, BCL2± . MYC+ in some cases of typical DLBCL, nos, and in BCL-U
• Germinal center B like	Hans: (CD10+) or (CD10−/bcl-6+/MUM1−) Choi: (GCET+/MUM1−) or (GCET−/CD10+) or (GCET−/CD10−/BCL6+/FOXP1−)
	Tally: Scoring system favors CD10, GCET, and LMO2 >30 %
• Non-germinal center B like	Hans: (CD10−/BCL6−) or (CD10−/BCL6+/MUM1+) Choi: (GCET+/MUM1+) or (GCET−/CD10−/BCL6+/FOXP1+) or (GCET−/CD10−/BCL6−)
	Tally: Scoring system favors MUM1, FOXP1, and LMO2 <30 %
Primary mediastinal (thymic) large B-cell lymphoma	CD19+, CD20+, CD22+, CD79a+, MAL+, cREL+, CD200, MUM1, CD23, BCL2±, BCL6±, CD30± (weak, heterogeneous), surface Ig weak to absent
Burkitt lymphoma	CD19+, CD20+, CD10+, BCL6+, BCL2-, monotypic sIg +, MUM1−, MYC+, Ki67 > 95 %. Cases associated with EBV: EBV-encoded RNA+/EBNA-1+ and LMP1−/EBNA-2−

2 Practical Points

Diagnosis of B-cell lymphoma is best achieved with excisional or incisional lymph node or extranodal tissue biopsy. Examination of the fresh biopsy tissue (by touch imprint or frozen section) clinically suspected of lymphomatous involvement at the time of the procedure allows proper allocation of fresh tissue for flow cytometry and cytogenetic studies. While fine-needle aspiration can result in procurement of fresh cells for ancillary flow cytometry testing, it is not ideal for definitive lymphoma classification since this requires assessment of spatial and architectural pattern recognition that is lost in FNA samples. Similarly, needle core biopsies may not show important architectural features and may result in a non-definitive diagnosis, misclassification, or even misdiagnosis. Formalin fixation is the standard, and through technical advances over the past 20 years, formalin-fixed paraffin-embedded tissues can now be used for detailed immunophenotyping by immunohistochemistry (essential in modern practice), fluorescence in situ hybridization for

Table 2 Recently investigated molecular biomarkers in selected B-cell non-Hodgkin lymphomas

	Molecular biomarker	Useful method for detection	Significance
Lymphoplasmacytic lymphoma	*MYD88* L265P mutation	Allele-specific PCR	Fairly sensitive and specific for LPL/WM and IgM MGUS diagnosis. May be predictive of disease burden and indicate risk of progression in IgM MGUS
Mantle cell lymphoma	SOX11 transcription factor overexpression	Immunohistochemistry (especially monoclonal anti-SOX11^{MRQ-58}, Cell Marque, Rocklin, CA)	Good biomarker for MCL diagnosis, including cyclin D1-negative variant. May be a useful prognostic parameter, but studies are conflicting. May be a promising prospect for MRD analysis. Suppresses terminal B-cell differentiation and drives angiogenesis in MCL [97].
Diffuse aggressive B-cell lymphoma	"double-hit" genotype (dual *BCL2* and *MYC* translocations are most common)	Fluorescence in situ hybridization (FISH) detects genetic translocation	Prognostic biomarker (worse progression-free and overall survival). Double-protein-positive (MYC and BCL2 protein by immunohistochemistry) independently predicts a worse survival in rituximab–CHOP-treated patients with DLBCL
Diffuse large B-cell lymphoma	Germinal center B cell-like (GCB) versus activated B cell-like (ABC) gene expression profile	Several immunohistochemistry—based algorithms, or new multiplex gene expression assay (ICEPlex® system, PrimeraDx, Mansfield, MA)	Prognostic and biologically significant. The ABC subtype has a worse outcome and indicates activation of the B-cell receptor and NF-κB pathways. This may also predict response to targeted therapies and support clinical trials

specific chromosomal rearrangements or numerical abnormalities, and DNA- or RNA-based testing (such as gene rearrangement, other amplification-based, expression, or sequencing studies). To summarize, excisional lymph node biopsy with a small portion sent for flow cytometric analysis provides the best guarantee of arriving at a specific diagnosis, particularly if an adequate lymphoid sample can be confirmed at the time of surgery.

3 Follicular Lymphoma

Follicular lymphoma (FL) is a common B-cell lymphoma that accounts for 20 % of non-Hodgkin lymphomas in the USA and Western Europe. It has a median age of 60 years and female predominance. Patients usually present with painless, slowly progressive lymphadenopathy and higher stage (Ann Arbor III–IV) with few exhibiting B symptoms. Despite its prototypic clinical course, it has been known for some time that the disease is variable with some patients experiencing waxing and waning symptoms, while others might succumb following early transformation to a high-grade lymphoma [47].

Histopathologically, this lymphoma subtype effaces the nodal architecture with at least a partially follicular pattern. The cytologic composition is a mixture of centrocytes and centroblasts in varying proportions, and grading is based on the number of centroblasts per 400× microscopic field (grades 1—3B). The phenotype is that of a germinal center B cell (GCB) with expression of BCL6, CD10, LMO2, and HGAL in most cases [40, 118]. The genetic features include clonally rearranged immunoglobulin genes and t(14;18)(q32;q21) that leads to aberrant *BCL2* expression. Alternatively, *BCL2* can be duplicated/amplified or translocated to one of the immunoglobulin light-chain genes, but the proportion of cases that have *BCL2* rearrangements decreases with increasing cytologic grade. The largest proportion of FL in North America and Western Europe has low-grade cytology, t(14;18)(q32;q21), and CD10 and BCL2 protein coexpression [37]. FISH seems to be the most sensitive method for detection of *BCL2* translocation [107].

FL is incurable but relatively indolent. The outcome can be predicted by the FL-specific International Prognostic Index (i.e., FLIPI), which was developed for all FL histologies, and includes a point system based on 5 factors (age > 60, stage III/IV, LDH > upper limit of normal, nodal groups > 4, and Hgb < 12 [96]. This was revised to the FLIPI-2 which was designed in the rituximab era and took into account the mass diameter size, as well as using progression-free survival as an endpoint instead of overall survival [25].

The clinical heterogeneity in FL was investigated by gene expression profiling. This led to the discovery of the importance of the microenvironment in predicting survival. Within a large cohort of FL, a survival predictor was generated based on genes that were found to reflect the nonmalignant immune cells (such as T cells, macrophages, and dendritic cells) that were flow sorted from the tumor [16]. A separate gene expression study using different selection criteria and endpoints found

differences between transformed and non-transformed FL, notably possession of an activated follicular hyperplasia versus a downregulated immune response signature, respectively. They also found that characterization of the immune state by immunohistochemistry was a sensitive way to assess the microenvironmental features [31]. However, there was little overlap in terms of a clinically useful gene set that could be exploited. Additional immunohistochemistry-based studies as a surrogate for GEP, in an attempt to characterize the immune cell composition (lymphoma-associated macrophages, "polarized macrophages," and T-cell helper or regulatory subsets) for prognostic benefit, yielded conflicting results, especially when this was extended to prospective studies of patients on monoclonal antibody therapy. Some were able to stratify groups based on outcome [102, 111], while others showed no association with immune makeup and overall survival [99]. Differences in results may be explained by differences in patient selection, treatment regimens, or technical issues. Regardless, there is evidence that the microenvironmental composition in FL shifts during disease progression and is likely important for tumor survival [50].

FL, along with other B-cell malignancies, possesses many genetic alterations that are being defined and characterized as to biologic and clinical significance. Recently, mutations in genes associated with chromatin modification (*EZH2*, 20 % of FL) and histone methytransferases (*MLL2*, 89 % of FL; *CREBBP*, 32 % of FL) were discovered using high-throughput sequencing technologies [61, 85]. *MLL2* has a high mutational frequency and was thus hypothesized to cooperate with other mutations to increase genetic instability. *CREBBP* mutation attenuates acetylation of *BCL6*, resulting in an increase in activity of that oncogene and altered expression of *BCL6* target genes [74]. Importantly though, to understand the significance of each mutation in lymphomagenesis, a pursuit of the clonal/subclonal architecture of FL demonstrated that *IGH@/BCL2* frequently underlies the disease (assumed to be the primary event), while *CREBBP* is a candidate driver mutation and an important secondary event. *MLL2* and *TNFRSF14* were considered tertiary accelerator mutations [35].

To summarize, the FLIPI remains the most widely used prognosticator for FL at diagnosis. Cytologic grade is not prognostic in many studies, but FL grade 3B (comprised almost entirely of large centroblasts) shares biologic features more akin to diffuse large B-cell lymphoma [41], and a recent large retrospective review found that FL grade 3B has a higher mortality and a distinctly different clinical course (more aggressive, but curable) in comparison with grades 1–2 and 3a [112]. Studies using array comparative genomic hybridization to detect DNA copy number alterations or using gene expression profiling revealing lesions of *TP53* or *CKND2A*, or increased *MYC* expression levels, have approximated risk of transformation. However, this is not routinely done, and risk is not consistently predictable for all samples, precluding its clinical utility [18, 27]. At present, there is no prospectively validated clinical tool with which to use gene expression profiling in FL to evaluate the microenvironment for prediction of prognosis. High-throughput sequencing is an avenue that will likely be utilized as a part of routine diagnostics in the near future, now that it is feasible on formalin-fixed paraffin-embedded tissues. Uncovering the clonal architecture of neoplasms can help to

identify therapeutic targets by helping to focus on what mutations might be subclonal (and less effective for a targeted therapy) as opposed to a founder, driver, or accelerator mutation [35]. These shed light on new targets for therapies such as demethylating agents, histone- or chromatin-modifying therapies, and small-molecule inhibitors but also might be powerful to predict whether a patient's individual tumor might be responsive to these therapies based on its stage of clonal evolution.

4 Lymphoplasmacytic Lymphoma

Lymphoplasmacytic lymphoma (LPL) is a small B-cell neoplasm of older adults that usually affects the bone marrow, and less often involves spleen or lymph nodes [101]. It is characteristically accompanied by a serum IgM monoclonal paraprotein. Clinically, it is associated with hyperviscosity and Waldenström macroglobulinemia (WM), defined as bone marrow involvement with monoclonal B cells of LPL type and serum IgM paraproteinemia at any level [73]. While the pathologic features can be distinctive, it shares features with other types of small B-cell lymphomas, and genetic abnormalities such as deletion of 6q occurring most commonly in LPL are neither sensitive nor specific in assisting the diagnosis [9].

Recently, whole-genome sequencing identified a recurrent somatic mutation in the myeloid differentiation response gene 88 (*MYD88* L265P) present in approximately 91 % of patients with WM, which is absent in multiple myeloma and rarely present in splenic marginal zone lymphoma (approximately 6 %) [29, 105]. The mutation itself was initially discovered in DLBCL (29 % of activated B-cell-like DLBCL vs. 1.4 % germinal center-like, and 9 % of gastric MALT lymphomas), where it was shown to promote cell survival via an IRAK kinase–protein complex leading to JAK-STAT3 activation, NF-KB signaling, and interleukin/interferon secretion [64]. It is prevalent among other types of aggressive B-cell lymphomas with an activated B-cell-like immunophenotype, such as primary central nervous system lymphoma [60] and primary cutaneous DLBCL, leg type [76].

The *MYD88* L265P is not entirely specific for LPL in small B-cell lymphomas. It can be identified using high-sensitivity allele-specific PCR in a small percentage of splenic marginal zone lymphoma and a very small minority of chronic lymphocytic leukemia, as well as one reported case of hairy cell leukemia. [22, 46, 69]. It is also present in 50–87 % of IgM MGUS [46, 54]. Aside from its use in diagnosis of LPL/WM, recurrent somatic mutations in WM such as *MYD88* and, to a lesser degree, in the more recently discovered chemokine receptor *CXCR4* (27 %) may determine clinical presentation, progression, and/or overall survival. For patients with IgM MGUS, presence of *MYD88* L265P was associated with greater disease burden and an increased risk of disease progression, such that it might prove to be a useful biomarker in evaluation of this disease [109]. The Bruton tyrosine kinase (BTK) inhibitor ibrutinib was shown to inhibit MYD88-BTK complexes and thus support lymphoplasmacytic cell survival in patients with WM [117]. Presence of the *CXCR4* mutation was shown to be associated with resistance to ibrutinib by

mediating signaling pathways resistant to growth suppression in the presence of CXCR4 ligand [11]. Nonetheless, in a phase I study, ibrutinib therapy showed promising results in patients with WM [2]. Detection of *MYD88* L265P in the peripheral blood of patients with WM and IgM MGUS by quantitative allele-specific PCR is an area of recent interest, as the delta Ct might predict disease burden in the bone marrow and might obviate the need for bone marrow aspiration/biopsy-based monitoring of patients with WM/IgM MGUS [116]. It may also have utility in minimal residual disease (MRD) assessment. Thus, *MYD88* L265P has proven its utility not only as a diagnostic marker, but as a biomarker for disease burden and/or progression, and it is a fairly simple assay to implement in a clinical laboratory setting.

5 Mantle Cell Lymphoma

Mantle cell lymphoma represents 2–8 % of non-Hodgkin lymphomas in the United States. It presents in the seventh decade (median age 63 years) and is characterized by a widespread nodal presentation (Ann Arbor stage III/IV) accompanied by B symptoms, with a high frequency of Waldeyer's tonsillar ring involvement, and often with splenic involvement. Some patients have gastrointestinal manifestations in the form of multiple intestinal lymphomatous polyposis. Staging bone marrow examinations are frequently positive, and occasionally, circulating lymphoma cells are identifiable by morphology and flow cytometric analysis [100]. The median survival has increased over the past 30 years and is now estimated to be 4–5 years. MCL is typified by a high response to frontline therapies with development of chemoresistance at the time of relapse [33].

Various histopathologic growth patterns of lymph node involvement include mantle zone, nodular, and diffuse, in addition to a relatively recently described, extremely rare "in situ" pattern of localization [1, 12]; Weisenburger et al. [113]. The neoplastic cells are monomorphous small lymphocytes with nuclear irregularities and scant cytoplasm, with a distinctive B-cell immunophenotype (CD19+, CD20+, sIg+, CD5+, CD10−, CD23− or subset+, IgM ±IgD, cyclinD1+). Less commonly, blastoid or pleomorphic variants with lymphoblast-like or centroblast-like cytologic features and numerous mitoses can occur, either de novo or as histologic progression of usual mantle cell lymphoma [72]. MCLs with a higher proliferative index as estimated by Ki-67 immunohistochemistry or by mitotic index have a worse overall survival, regardless of the cytologic variant [103].

The genetic hallmark of mantle cell lymphoma is t(11;14)(q13;q32). As a result of this translocation, the cyclin D1 gene (*CCND1*) on chromosomal region 11q13 is translocated into the *IGH@* locus, where it comes under regulatory control of the *IGH@* enhancer sequences, resulting in overexpression of cyclin D1 protein [93]. This leads to constitutive cell cycle dysregulation, which together with secondary alterations in DNA damage response and with activation of cell survival signals underlies the pathogenesis of MCL. Less often, other partner loci such as either of

the immunoglobulin light-chain genes (κ, 2p11; λ, 22q11) are joined to *CCND1* [51]. While an in-depth discussion of cyclin D1-negative mantle cell lymphoma is beyond the scope of this chapter, it is an increasingly studied variant that can be recognized by typical morphologic and phenotypic features of MCL and a shared global genomic profile, with the exception of cyclin D1 [28]. A recent study found that in over half of the cyclin D1-negative MCL variants, a *CCND2* rearrangement was detected predominantly involving one of the Ig light-chain genes. Still, the molecular mechanism for cyclin D1-negative mantle cell lymphomas is only partially revealed. The clinical and biologic behavior of the cyclin D1-negative mantle cell lymphomas was similar to that of conventional MCL, indicating that CCND2 rearrangement can be a biomarker that indicates a need for intensive chemotherapy [88]. In addition to cyclin D1 translocation, there are numerous secondary genetic alterations in mantle cell lymphoma that contribute to its pathogenesis including deletion of the 9p21 locus (thereby *CKDN2A* and affecting cell cycle control via INK4a/CDK4/RB1), point mutation or deletion of *RB1* or *TP53*, other gene amplification, or *ATM* deletion contributing to genomic instability [45]. Finally, somatic mutational data generated by whole-genome or exome sequencing technologies have identified significantly mutated genes in MCL including known drivers of pathogenesis and others that play a role in anti-apoptosis or chromatin modification. *NOTCH2* mutations were discovered and correlated with a poor prognosis. Additional studies are needed to further understand mutational profiles in the setting of disease progression and significance for biologic therapies [6].

The Mantle Cell Lymphoma International Prognostic Index (MIPI) can accurately stratify patients into low-, intermediate-, and high-risk groups. Assessment of the tumor cell proliferative index by Ki67 yielded valuable prognostic information independent of the MIPI, but combined with the prognostic index, a "biologic MIPI" can serve as a prognostic guide for risk-adapted therapy [20, 42]. So far, TP53 appears to be the only significant independent molecular marker to add additional prognostic value to the MIPI in multivariate analysis [66].

While mantle cell lymphoma is typified by overall short survival and relatively aggressive disease course, it is now recognized that an indolent form of mantle cell lymphoma exists. It can be identified clinically as a subgroup of patients with non-nodal disease who may present with splenomegaly and leukemic involvement. This has been associated with mutated IGVH genes and lack of CD38 expression [70]. These patients have been shown to have a favorable prognosis with a median survival of 79 months compared to a group of nodal-based lymphoma with median OS of 30 months [70]. Indeed, patients with what could be considered a monoclonal B-cell lymphocytosis with t(11;14) have been identified [68]. Furthermore, we now realize that patients do not need to be treated at diagnosis and may do well with a "wait and watch" strategy [58]. Several independent studies have identified recurrent biologic and clinical features that may identify this indolent subtype, including non-nodal leukemic presentation, hypermutated immunoglobulin heavy-chain variable genes (IGVH, indicating derivation from post-GCBs), simple karyotype, and stable disease with longer survival [70, 84]. These features were reinforced by gene expression profiling in a study that identified a molecular

signature of 13 genes that was highly expressed in conventional mantle cell lymphoma as compared to indolent MCL. Within the gene set, the transcription factor SOX11 was particularly overexpressed in conventional mantle cell lymphoma and confirmed by protein expression [26]. A separate outcomes-based study divided patients into groups based on degree of IGHV mutations from germline. There was a significant difference in overall survival between those with high and low mutational load. The highly mutated cases had a better survival, were preferentially SOX11 negative, had lower genomic complexity, and were more often non-nodal in disease distribution [63]. Furthermore, studies of patients with a monoclonal B-lymphocytosis-like presentation of cyclin D1-positive MCL were more often SOX11 negative as compared with symptomatic, nodal cases [24, 68].

While most cohorts of indolent patients showed a predilection for SOX11 negativity, a population-based cohort study published conflicting results with a shorter overall survival in SOX11-cases, but the significance was lost on multivariate analysis [67]. Another study among patients treated with dose-intensive (i.e., hyper-CVAD based) regimens found that high SOX11 expression was associated with improved survival [52]. Lack of uniformity among studies and difference in selection criteria of indolent populations add to the difficulty in drawing an overall conclusion from these data.

SOX11 has been recognized in the last several years as a reliable biomarker in identification of mantle cell lymphoma as well as the cyclin D1-negative conventional or blastoid variants [21, 62, 120]. Several new monoclonal antibodies are commercially available to incorporate into routine diagnostic practice [97]. It has been suggested that SOX11 by itself should not be considered to be a prognostic parameter but rather used as a biomarker that may help to recognize either cyclin D1-negative MCL or a subtype of MCL with different biologic and clinical features. Nonetheless, study of SOX11 target genes is an active area of interest and it remains to be determined whether SOX11 could be a useful prognostic marker.

With a broad range of treatment options for patients with small B-cell lymphomas, some patients achieve a long-lasting remission. However, the majority suffer a relapse that might be heralded by very low levels of residual lymphoma cells. Detection of MRD has been expanded from acute lymphoblastic leukemia to B-cell lymphomas, including MCL, in an increasingly important tool for risk prediction [77]. This can be achieved via various modalities including flow cytometric analysis, reporting sensitivities of approximately 10^{-3} [8]. PCR-based methods have made great strides in achieving optimal sensitivity. Real-time quantitative PCR using allele-specific primer design has standardization guidelines [108] and a high sensitivity (10^{-5}), superior to the sensitivity of immunoglobulin heavy-chain PCR analysis using consensus primers and overcoming inherent limitations such as ongoing somatic mutation [10]. An ideal, MCL-specific target is the t(11;14) translocation, which can be highly sensitive (10^{-5}) by nested PCR, but the translocation is PCR detectable in only 25–40 % of cases [4, 36]. A promising prospect, SOX11, as a MRD marker for MCL was studied using mRNA-specific quantitative PCR (qPCR) technology in longitudinal peripheral blood samples of MCL patients. The researchers were able to correlate quantifiable level of SOX11

expression with clinical status and with level of t(11;14) by qPCR. Still, patient selection and validation over larger cohorts of patient groups will be required before this could be considered for clinical use [95].

In summary, cyclin D1 and SOX11 remain good biomarkers for the diagnosis of MCL, including cyclin D1-negative MCL. The MIPI is a good clinical risk stratification tool, and assessment of proliferation and TP53 provide added prognostic information. Further work on defining additional useful prognostic biomarkers will require validation in uniformly treated patient populations.

6 Diffuse Large B-Cell Lymphoma, Not Otherwise Specified

This section covers diffuse large B-cell lymphoma (DLBCL), which represents the most common type of non-Hodgkin lymphoma (30–40 % of adult non-Hodgkin lymphomas) and can arise de novo or from transformation of a preexisting low-grade lymphoma. Patients usually present with a rapidly enlarging mass that is FDG avid on positron emission tomography imaging. Occurrence at lymph node sites is most common, but it can arise in virtually any location in the body and is common at extranodal sites such as the gastrointestinal tract or skin. Patients are most often treated with anthracyclin-containing multiple-agent chemotherapy regimens that include rituximab, and there is an approximately 55 % 5-year survival [65], but there is much variability in that percentage depending on other prognostic factors. The International Prognostic Index (IPI) is a valuable tool that can separate patients in distinct prognostic risk groups [94], and it has been revised and validated in the rituximab era [92].

From a morphologic standpoint, the recognized variants of DLBCL, not otherwise specified (NOS), include centroblastic, immunoblastic, and anaplastic. Rarer variants also exist and are important for recognition by the pathologist. The immunoblastic variant (being composed of at least 90 % immunoblasts) has been associated with poorer event-free and overall survival [7]. Other special categories of large B-cell lymphoma (without plasmablastic features) that are beyond the scope of this discussion include T cell/histiocyte-rich large B-cell lymphoma, primary DLBCL of the central nervous system, primary cutaneous DLBCL, leg type, EBV-positive DLBCL of the elderly, DLBCL associated with chronic inflammation, lymphomatoid granulomatosis, and intravascular large B-cell lymphoma, along with other categories of large B-cell lymphoma in association with immunodeficiency.

To better understand the heterogeneity of this lymphoma, gene expression profiling has identified “cell-of-origin” molecular subgroups of DLBCL that are similar to the profiles of different normal B-cell counterparts. One subgroup retained the gene expression program of the GCB and was thus termed “GCB like,” while the other group expressed genes that were induced during activation of peripheral blood B cells (“activated B cell like,” ABC) [3]. Aside from providing

insight into additional molecular alterations and activated pathways within the subgroups, distinct differences in overall survival between patients with GCB versus ABC subgroups were observed. The ABC type was shown to have an inferior outcome compared with the GCB type, even in the rituximab era. The subgroup occurs in an older proportion of patients (>70 years) and has biologic significance for sustained activation of the NF-κB pathway [55]. Since then, subsequent studies have validated this classification approach with large numbers of patients and have selected smaller gene sets to identify groups [14, 82, 91, 115]. To more easily identify a molecular subtype, immunohistochemical staining algorithms were developed based on the results of gene expression profiling [13, 38, 59]. When performed in qualified laboratories, these algorithms can show very good concordance with the GEP classifier [81]. The COO concept as a prognostic biomarker is relevant with modern immunochemotherapy [82, 110]. However, in addition, it may gain added relevance as a predictive marker. Given that the ABC-like DLBCLs demonstrate mutations that activate the B-cell receptor signaling pathway and ultimately NFkB, development of targeted therapies with preferential activity in the ABC subtype may call for knowledge of COO subtype in order to assist in therapy selection. Preliminary data support this approach, and trials are underway and in the planning phases that require COO determination as part of eligibility requirements [114].

Recent attention has been drawn to the importance of translocations involving *MYC*, *BCL2*, and *BCL6*. Apart from identifying some cases of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BL, see below), these translocations may have prognostic significance in DLBCL, NOS. The most frequent genetic finding in DLBCL, NOS, is a rearrangement of *BCL6* (3q27, 30–40 %), which occurs more often in the ABC subgroup, whereas *BCL2* and *MYC* translocations are usually associated with GCB DLBCL. In particular, *MYC* translocations occur in approximately 10 % of DLBCL and portend a dismal prognosis, either as a single genetic insult or as additional hits involving *BCL2*/*MYC*, *BCL6*/*MYC* ("double-hit lymphomas"), or the rare *BCL2*/*BCL6*/*MYC*-rearranged "triple-hit" lymphomas [5]. This includes cases with *IGH@BCL2*/t(14;18)(q32;q21) plus extra *MYC* signals or amplification, as well as cases with *MYC* rearrangements with extra *BCL2* copies [57]. However, there is still controversy as to whether *MYC* rearrangements in DLBCL are truly an independent predictor of prognosis. Studies of risk stratification in patients treated with rituximab–CHOP found confirmed *MYC* translocation as predictive of progression-free survival and overall survival on multivariate analysis [89] and also showed a significant association with treatment resistance [106]. Similarly, a Southwest Oncology Group Study of high-grade morphologic features and MYC protein expression by immunohistochemistry [15] found MYC to be a poor prognostic factor on multivariate analysis and independent of morphology, highlighting the importance of staining for this protein in routine clinical practice. However, other studies have questioned the prognostic power of MYC as a single abnormality. In one study examining BCL2 and MYC protein expression, the prognostic impact of *MYC* was due to the confounding effect of BCL2/MYC double-protein-positive

cases, and *MYC* positivity alone did not impact overall survival [43]. Another study showed that isolated *MYC* rearrangements have weaker prognostic relevance than isolated *BCL2* translocations [110]. In an attempt to clarify this issue, a recent systematic review and meta-analysis that included 24 enrolling clinical trials confirmed the prognostic relevance of isolated *MYC* aberrations (including amplifications) in terms of both protein and mRNA expression; however, interpretation of the data is challenged by the heterogeneity of the included studies [121].

More recently, it was found that MYC and BCL2 protein coexpression predicts survival in patients with DLBCL that are treated with rituximab (R)–CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). While high MYC protein expression by IHC is often (but not invariably) associated with a *MYC* translocation (and thus an adverse risk), the negative impact of MYC protein expression on progression-free and overall survival was shown only when BCL2 protein was coexpressed. This was significant even after adjusting for high-risk features in the IPI score [48]. The practical use of an immunohistochemical "double-hit score" was demonstrated in a study that validated shorter overall and progression-free survival in patients with high BCL2/MYC protein coexpression independent of other variables and was able to identify patients with high-risk "double-hit biology" from within an independent cohort of DLBCL [34]. When examining these biomarkers in DLBCL patients according to the cell of origin, the level of positive protein expression was a strong independent predictor of overall survival in patients with GCB, but not the non-GCB subtype DLBCL, with high BCL2 (>30 %) and MYC (>50 %) coexpression correlating with the worst outcome [75]. Because of its wide availability, assessment of BCL2 and MYC expression by immunohistochemistry is becoming a routine part of the pathology report to provide additional prognostic information to clinicians.

7 Primary Mediastinal Large B-Cell Lymphoma

Primary mediastinal large B-cell lymphoma (PMBL) arises within the mediastinum from B cells of probable thymic origin. Patients are young adults with a median age of 35 and a female predominance. They may present with a bulky anterosuperior mediastinal mass that can secondarily invade nearby organs such as lungs or directly extend to local lymph nodes, but it rarely disseminates. It is important to exclude primary lymph node involvement at other sites, as well as bone marrow involvement, to avoid misdiagnosis of a systemic DLBCL that might secondarily involve the mediastinum [30].

The microscopic features of this lymphoma type vary from case but can take the form of a diffuse proliferation of intermediate to large cells with a moderate amount of clear cytoplasm and either ovoid or sometimes slightly more pleomorphic nuclei. Compartmentalizing alveolar sclerosis is a prominent feature in many cases. The phenotype includes most B-cell antigens including IRF4/MUM1, positive for CD23, with low to absent immunoglobulin and CD10 expression, sometimes

heterogeneous/weak CD30 expression, and MAL antigen. Frequent karyotypic abnormalities include chromosomal aberrations for 2p16.1, 9p24.1, and 8q24 [71]. A large study of B-cell lymphomas demonstrated rearrangement of the MHC class II transactivator *CIITA* (16p13.13) in PMBL (29/77, 38 %) [98]. The implication of such an aberration might be that the tumor can then escape from immune surveillance by downregulation of HLA class II associated proteins, among other mechanisms. An association was found between *CIITA* gene fusions, and reduced HLA-DR protein expression was demonstrated [23]. Additional research is needed to identify biomarkers for prognosis in PMBL, though one recent study found MUM1 protein expression to correlate independently with a decreased overall survival [19].

It recognized that some lymphomas have combined features of both classical Hodgkin lymphoma and DLBCL, particularly nodular sclerosis classical Hodgkin lymphoma and PMBL [104]. Furthermore, some patients were reported to develop large B-cell lymphoma after treatment for Hodgkin lymphoma, while others reported composite Hodgkin/large B-cell lymphoma, and thus the designation "mediastinal gray-zone lymphoma" [32, 119]. While PMBL lacks truly distinctive morphologic features that might otherwise distinguish it from conventional DLBCL, identification of gene expression signature unique to this entity was pivotal in the molecular classification of large B-cell lymphoma. In fact, when gene expression profiling was used to establish a more precise molecular diagnosis of PMBL, it emerged as an entity that primarily affected younger patients and identified a subgroup with a better prognosis compared to other DLBCLs. Gene profiling supported the suspected relationship between PMBL and Hodgkin lymphoma in that over one-third of the genes that were part of the PMBL signature were characteristic of Hodgkin lymphoma cells [83]. Furthermore, the epigenetic profile of PMBL was found to be distinct and separate from DLBCL, and analysis of methylation patterns supported an intermediate position between DLBCL and classical Hodgkin lymphoma [23].

8 Burkitt Lymphoma

BL is a highly aggressive mature B-cell neoplasm that makes up 40 % of non-Hodgkin lymphomas in youth under age 20. It presents as a rapidly enlarging mass, commonly involving extranodal sites, and exists in three different clinical variants. The endemic form predominantly affects young children in equatorial Africa and is usually associated with Epstein-Barr viral infection, and the tumors are often localized to the jaw or facial bones, kidneys, or abdominal region. The sporadic type occurs in a broad geographic distribution that includes North America and European countries, and often affects the abdomen or terminal ileum of immunocompetent children. The third type is immunodeficiency related, and it is known for its association with HIV. Rarely, a leukemic phase exists, either in patients with

bulky disease or very uncommonly as a de novo peripheral blood/bone marrow leukemia phenomenon [56].

The neoplastic infiltrate is composed of intermediately sized, monotonous B cells with numerous mitoses and tingible body macrophages imparting a "starry sky" appearance. BL cells resemble germinal center centroblasts by cytomorphologic grounds and express pan B-cell antigens and surface immunoglobulin, plus CD10 and BCL6. BCL2 is characteristically negative or only weakly positive [86].

The vast majority of cases have a detectable *MYC* translocation (8q24) to the immunoglobulin heavy-chain region (14q32), or to the kappa light-chain gene (2p11) or lambda-chain gene (22q11). In some cases, a *MYC* cannot be demonstrated by FISH, but in these cases, differences in the *MYC* breakpoint or subdetectable insertions/deletions in the *MYC* gene may elude detection. Thus, a negative test result does not exclude the diagnosis. Similarly, it is important to remember that other types of lymphomas can harbor a *MYC* rearrangement, such as DLBCL discussed previously, as well as mantle cell lymphoma and FL can acquire a *MYC* translocation as it transforms to a more aggressive tumor [18, 39].

Gene expression profiling has revealed a distinct molecular phenotype for BL [17] and that BL can be identified with certainty on the basis of a number of MYC target genes, involved in germinal center differentiation, NF-KB activation, and MHC class I molecules [44]. The genetic makeup of BL was further elucidated by using deep sequencing technologies which identified *ID3* as an important tumor suppressor gene in BL that appears to serve as a negative regulator of *MYC* [80, 90].

9 B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between Diffuse Large B-Cell Lymphoma and Burkitt Lymphoma

The WHO 2008 category of B-cell lymphoma, unclassifiable, incorporates cases with morphologic, immunophenotypic and genetic features that are intermediate between DLBCL and BL (WHO 2008 classification). The existence of this category is supported by gene expression and karyotypic/genomic profiling, which can identify a "molecular Burkitt" signature [17, 44, 87]. Classification of these cases at the practice level is problematic, since the tools used to define them are not readily available in clinical laboratories. These types of case were likely included in former designations such as "small non-cleaved, non-Burkitt" (Working Formulation), "atypical Burkitt lymphoma," and "high-grade B-cell lymphoma, Burkitt-like" (Revised European and American Lymphoma Classification) or were loosely referred to as "DLBCL with high-grade features," "gray-zone lymphoma," or "diffuse aggressive B-cell lymphoma." Genetically defined "double-hit" lymphomas are included in this category of B-cell lymphoma, unclassifiable (BCL-U) [49]. These can be recognized with currently available clinical laboratory tests such as FISH testing. Thus, assessment of *MYC, BCL2*, and *MYC* translocation should be performed in all diffuse aggressive B-cell lymphomas suspected of being a double-

hit lymphoma. One practical way to screen is to perform MYC IHC given its ability to predict presence of *MYC* translocation and to perform FISH confirmation (for all three targets) in cases with high nuclear MYC (>40–50 %) expression.

This still leaves a difficult group of cases that belong to this category for which we cannot yet definitively recognize by current laboratory tests. The category should then be used only for cases in which the clinical, morphologic, phenotypic, and/or genetic evidence cause a truly inscrutable diagnostic conundrum between DLBCL and BL [79]. An example may be cases with morphologic features suggestive but insufficient for BL in which a BL-like (CD10+/BCL2 weak-negative) phenotype is seen, in the setting of a demonstrated immunoglobulin gene/*MYC* translocation with complex karyotype.

10 Next-Generation Sequencing for Minimal Residual Disease Monitoring and Mutation Detection

Many advances have been made in the treatment of B-cell lymphoma, and a need exists for post-treatment assessment and monitoring of treated patients as a means to identify an early relapse or predict the potential for relapse. MRD can be detected by cytogenetics, flow cytometry, or PCR-based methods. PCR-based MRD detection by detection of immunoglobulin heavy-chain and/or T-cell receptor gene rearrangements using tumor-specific primers has potential to be a sensitive means of assessment [78]. Next-generation sequencing was shown to be a feasible tool in MRD detection in MCL, with comparable results to real-time quantitative PCR [53]. Identification of an ideal MRD marker/target is of utmost importance in establishing a useful assay, and difficulties might arise due to ongoing somatic hypermutation or clonal evolution. Certainly, next-generation sequencing on routine patient samples will be feasible in the next several years, and it may provide valuable diagnostic information and prognostic information and help guide individualized therapies by identifying biologic pathways that can be targeted with new therapies. The challenge will be to refine them for use in routinely processed tissues and apply these techniques to highly annotated clinical data sets in order to begin to rationally use this complex data for prognosis and prediction.

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